ACUTE OBLITERATING BRONCHIOLITIS.

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Abstract: in this article we talk about bronchiolitis obliterans , also known as obliterative bronchiolitis, constrictive bronchiolitis and popcorn lung, is a disease that results in obstruction of the smallest airways of the lungs (bronchioles) due to inflammation. Symptoms include a dry cough, shortness of breath, wheezing and feeling tired.

Keywords: obliterative bronchiolitis, constrictive bronchiolitis, popcorn lung,

Obliterating bronchiolitis (constrictive bronchiolitis) is a severe respiratory disease caused by persistent progressive inflammatory and/or fibrous obstruction of the bronchioles (terminal sections of the bronchial tree).Bronchiolitis is an acute inflammatory disease of the lower respiratory tract, in which blockage of the bronchioles (small bronchi) occurs, which makes breathing difficult, especially exhalation. Most often this disease occurs in children under the age of two years, the peak incidence occurs at the age of two to six months. Due to the polyethologicity of pathology, experts consider it as a nonspecific reaction of the tissues of small elements of the respiratory system to the effects of various damaging agents.

Diagnostics. The diagnosis of obliterating bronchiolitis is complicated by the development of nonspecific symptoms and is based on the collection of anamnesis, clinical manifestations, physical examination data, radiography and computed tomography of high-resolution chest organs, functional tests, results of cytogram of bronchoalveolar flushing, as well as histological examination of lung tissue.

Treatment. Difficulties in making a diagnosis, rapid progression and irreversibility of changes in the bronchial wall significantly limit the possibilities of therapy, which is reduced to preventing further development of the inflammatory process and fibrous proliferation in small parts of the respiratory system and stabilizing the patient's condition. Treatment of this pathology is based on the use of corticosteroids in combination with immunosuppressants. Inhalation therapy may also be prescribed to the patient, which will reduce the need for systemic glucocorticoids by achieving higher concentrations of the drug in the tissues. With the infectious etiology of obliterating bronchiolitis in the acute phase of the disease, the use of antiviral or antibacterial agents may be required. Post-infectious bronchiolitis in most cases occurs in children and is associated with infections caused by adenovirus, respiratory syncytial virus, cytomegalovirus, parainfluenza virus or herpes infection. Sometimes the development of acute obliterating bronchiolitis may be associated with other pathogens, for example, mycoplasma, klebsiella, legionella, fungi of the genus aspergillus, HIV infection. In some cases, inhalation obliterating bronchiolitis occurs when inhaling toxic gases, acid vapors, organic and inorganic dust, nicotine or cocaine. Drug-induced obliterating bronchiolitis occurs as a result of taking certain medications, such as cephalosporins, penicillins, sulfonamides, amiodarones, gold preparations and cytostatics.Idiopathic forms of the disease include cases of the disease that arose against the background of diffuse connective tissue diseases, Stevens-Johnson syndrome, exogenous allergic alveolitis, aspiration pneumonia, inflammatory lesions of the digestive tract, malignant histiocytosis and lymphoma.Posttransplantation obliterating bronchiolitis is found in about 20, and according to some data 50% of patients who have undergone organ and tissue transplantation.

Symptoms. Obliterating bronchiolitis is characterized by an acute or subacute course. Patients experience symptoms of general intoxication, such as weakness, malaise, high fever or subfebrile fever. A typical manifestation of the disease is the presence of a dry obsessive cough, increasing expiratory dyspnea, first with physical exertion, and then at rest.At the initial stage of the development of the pathological process, dry whistling is detected, and over time, small-bubbly wheezing, which can sometimes be heard at a distance. With the passage of time, the weakening of breathing, the swelling of the chest joins. With obliterating bronchiolitis, hemoptysis occurs only in severe pathology. As the course of the disease worsens and the development of the pulmonary heart, signs of respiratory failure and pulmonary hypertension appear.

Obliterating bronchiolitis (OB) is a rare disease from the group of "diseases of the small respiratory tract", in which bronchioles are affected – the respiratory tract (DP) with a diameter of less than 2-3 mm, which do not have a cartilaginous base and mucous glands [1]. There are terminal and respiratory bronchioles. Terminal (membranous) bronchioles belong to the air-conducting (conductive) DP, their wall contains smooth muscle cells. Each secondary pulmonary lobule contains from 4 to 8 terminal bronchioles with their corresponding primary lobules (acinuses) (K. Garg et al. 1994). The wall of respiratory bronchioles contains ciliated epithelial cells and alveolocytes and does not have smooth muscle cells, therefore respiratory bronchioles belong to transitional DP, i.e. they take part in both air and gas exchange. The concept of "small DP" began to develop thanks to J. Hogg et al. (1968), in whose studies the resistance of DP was measured using retrograde catheter technique. As it turned out, the share of small DP, the total cross–sectional area of which (53 – 186 cm3) is many times larger than the area of the trachea (3 – 4 cm3) and large bronchi (4 - 10 cm3), accounts for only 20% of the total resistance of DP. Therefore, the defeat of bronchioles in the early stages may be asymptomatic and not accompanied by changes in traditional functional tests; changes are noted, as a rule, already with a far-reaching lesion of small DP.

The frequency of the development of OB is not precisely established. According to J. LaDue [3], OB was detected only in one case out of 42 thousand autopsies, and in the study by K. Hardy et al. [4], devoted to the analysis of 3 thousand pediatric autopsies, in 7 cases. It is believed that at least 2-4 OB patients pass through a large pulmonological university center per year [5].

The first classical description of OB was made in 1901 by W. Lange, who examined in detail the morphological picture of the lungs of two patients who died from rapidly progressive respiratory failure. However, for several decades there has been practically no mention of this disease. In 1977, D. Geddes et al. described the clinical and morphological picture of OB as one of the variants of lung damage in rheumatoid arthritis.Perhaps, the greatest attention to this problem began to be paid after work. Epler , who analyzed about 2,500 open lung biopsy samples performed over 30 years at the University Hospital of Boston, and found 67 cases of OB. In 10 samples, a pattern of lesions of only terminal and respiratory bronchioles was revealed, i.e. "classic" or isolated bronchiolitis, and in 57 cases, along with bronchiole damage, a peculiar pattern of involvement in the inflammatory process of the alveoli with the presence of organized exudate in their lumen was observed – this syndrome was called "obliterating bronchiolitis with organizing pneumonia". OBOP was presented as a new clinical and morphological syndrome, different from isolated OB, idiopathic fibrosing alveolitis or ordinary interstitial pneumonitis. Shortly before G. Epler a similar syndrome was described by A. Davison et al., however, they used the term "cryptogenic organizing pneumonitis" – COP. As it turned out, despite the same terms, the clinical and morphological syndromes described by D. Geddes and G. Epler are inherently

completely different types of pathology. The OB examined by D.Geddes belongs to the group of obstructive diseases of small DP, is characterized by a clinical picture of continuously progressive dyspnea, an X-ray picture of increased transparency of pulmonary fields, a lack of response to steroids and a poor prognosis.

The OBOP described by G.Epler belongs to the group of interstitial lung diseases (ISL), is characterized by the short presence of cough, shortness of breath, fever, weakness, X-ray picture of scattered spotted infiltrates in the lungs, a good response to steroids and a favorable prognosis.The need for a clear distinction between these two diseases has caused numerous discussions on the pages of leading medical journals. In order to avoid terminological confusion, it was proposed to use the term "constrictive bronchiolitis", introduced in 1973 by B. Gosink et al., as a synonym for "isolated" OB, and the terms "cryptogenic organizing pneumonitis" and "proliferative bronchiolitis", first proposed respectively .

Along with OB and OBOP, other, also quite rare diseases of small DP are known: diffuse panbronchiolitis is a disease of residents of the Pacific region, characterized by damage to the sinuses, bronchioles, the development of bronchiectasis, colonization of Pseudomonas aeruginosa, a steady increase in respiratory failure ; respiratory bronchiolitis associated with ISL is a lung disease associated exclusively with smoking accompanied by unexpressed symptoms of shortness of breath and cough, well amenable to steroid therapy or self-resolving when quitting smoking.

The reasons for this are quite diverse. This disease usually occurs after transplantation of the heart – lung complex, two or one lung, bone marrow , after viral infections , inhalation of toxic substances , against the background of diffuse connective tissue diseases , inflammatory bowel diseases ,against the background of taking certain medications , radiation therapy, Stevens–Johnson syndrome , IgA nephropathy. The main reasons for this are listed in Table 1. In most cases, it is possible to find out the cause of the development of OB, idiopathic or cryptogenic forms are less common . The most well-studied forms of OB developed after transplantation.

It is believed that OB is a manifestation of nonspecific tissue reactions to various damaging stimuli at the level of small DP. After damage to the bronchial epithelium, mesenchymal cells migrate and proliferate into the lumen and wall of the bronchioles, which ultimately leads to the deposit of connective tissue in them.

The primary event in OB is often necrosis of the bronchiolar epithelium and denudation of the basement membrane in response to damaging stimuli (toxic fumes, viruses), which leads to excessive production of various regulatory peptides: growth factors, cytokines and adhesive molecules. In autoimmune, medicinal, and posttransplant diseases, the primary link in pathogenesis may be an increase in the expression of MHC antigens (major histocompatibility complex – the main histocompatibility complex) of class II on bronchiolar epithelial cells, which is the result of local cytokine production . These disorders lead to the presentation of autoantigens, T-cell activation, the development of inflammation and fibrosis in small DP, i.e. the same chain of events develops as in many other autoimmune diseases.

Sometimes there is a discontinuous course of pathology due to alternating periods of deterioration and relative stabilization of the condition, but complete recovery does not occur. In the late stages of obliterating bronchiolitis, the patient shows cyanosis and pronounced tension of the auxiliary respiratory muscles of the neck when breathing. Platelet growth factor (TFR) is considered to be one of the most likely growth factors involved in stimulating fibroblast proliferation in OB. An increase in the content of TFR was detected in bronchoalveolar lavage

(BAL) in patients with active OB (M. Hertz et al., 1992). Among cytokines, g-interferon (g-IFN) and interleukin 1b (IL–1b) play an important role in OB, the gene expression of which is increased in this disease .IL 1-b regulates the growth of lymphocytes, their differentiation and cytotoxicity in autoimmune and infectious processes, and g-IFN induces the expression of MHC class II antigens on epithelial cells and regulates the production of immunoglobulins. Epithelial cells play an important role in the pathology of OB. They secrete fibronectin, which is a chemoattractant for fibroblasts. Regenerating epithelial cells are able to enhance the proliferation of fibroblasts and the production of extracellular matrix components. In recent years, more and more attention has been paid to the study of the role of integrins in fibroproliferative processes, since integrins perform the function of adhesion of mesenchymal cells to the components of the extracellular matrix. The main cellular components of granulation tissue are fibroblasts and endothelial cells, and the main extracellular matrix proteins are fibronectin and fibrin/fibrinogen [19]. The adhesion of cells to fibronectin occurs with the help of a5b1 -integrin, to fibrinogen – with the help of a5b3 -integrin. Blockade of matrix cell adhesion processes can inhibit fibrogenesis reactions and prevent the development and progression of OB, therefore, the possibility of interfering with the inflammatory process at this stage is being studied .

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